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Pl. recd & spec. as follows
THF 1624

SUBSTITUTED ARYL COMPOUNDS AS NOVEL CYCLOOXYGENASE-2 SELECTIVE INHIBITORS, COMPOSITIONS AND METHODS OF USE

RELATED APPLICATIONS

This application is a divisional of U.S. Application No. 10/024,046 filed December 21,
5 2001, now allowed, which claims priority to U.S. Provisional Application No. 60/256,932 filed
December 21, 2000.

FIELD OF THE INVENTION

The invention describes novel substituted aryl compounds that are cyclooxygenase 2
(COX-2) selective inhibitors and novel compositions comprising at least one cyclooxygenase 2
10 (COX-2) selective inhibitor, and, optionally, at least one compound that donates, transfers or
releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels
of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase, and/or,
optionally, at least one therapeutic agent. The invention also provides novel kits comprising at
least one COX-2 selective inhibitor, and, optionally, at least one nitric oxide donor, and/or,
15 optionally, at least one therapeutic agent. The novel cyclooxygenase 2 selective inhibitors of the
invention can be optionally nitrosated and/or nitrosylated. The invention also provides methods
for treating inflammation, pain and fever; for treating and/or improving the gastrointestinal
properties of COX-2 selective inhibitors; for facilitating wound healing; for treating and/or
preventing renal toxicity or other toxicities; for treating and/or preventing other disorders
20 resulting from elevated levels of cyclooxygenase-2; and for improving the cardiovascular profile
of COX-2 selective inhibitors.

BACKGROUND OF THE INVENTION

Nonsteroidal anti-inflammatory compounds (NSAIDs) are widely used for the treatment
of pain, inflammation, and acute and chronic inflammatory disorders such as osteoarthritis and
25 rheumatoid arthritis. These compounds inhibit the activity of the enzyme cyclooxygenase
(COX), also known as prostaglandin G/H synthase, which is the enzyme that converts
arachidonic acid into prostanoids. The NSAIDs also inhibit the production of other
prostaglandins, especially prostaglandin G₂, prostaglandin H₂ and prostaglandin E₂, thereby
reducing the prostaglandin-induced pain and swelling associated with the inflammation process.
30 The chronic use of NSAIDs has been associated with adverse effects, such as gastrointestinal
ulceration and renal toxicity. The undesirable side effects are also due to the inhibition of
prostaglandin in the affected organ.

ABSTRACT OF THE DISCLOSURE

The invention describes novel substituted aryl compounds that are cyclooxygenase 2 (COX-2) selective inhibitors and novel compositions comprising at least one cyclooxygenase 2 (COX-2) selective inhibitor, and, optionally, at least one compound that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase, and/or, 5
optionally, at least one therapeutic agent, such as, steroids, nonsteroidal antiinflammatory 10 compounds (NSAID), 5-lipoxygenase (5-LO) inhibitors, leukotriene B₄ (LTB₄) receptor antagonists, leukotriene A₄ (LTA₄) hydrolase inhibitors, 5-HT agonists, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors, H₂ antagonists, antineoplastic agents, 15 antiplatelet agents, thrombin inhibitors, thromboxane inhibitors, decongestants, diuretics, sedating or non-sedating anti-histamines, inducible nitric oxide synthase inhibitors, opioids, analgesics, *Helicobacter pylori* inhibitors, proton pump inhibitors, isoprostanе inhibitors, and mixtures thereof.. The invention also provides novel kits comprising at least one COX-2 20 selective inhibitor, and, optionally, at least one nitric oxide donor, and/or, optionally, at least one therapeutic agent. The novel cyclooxygenase 2 selective inhibitors of the invention can be optionally nitrosated and/or nitrosylated. The invention also provides methods for treating inflammation, pain and fever; for treating and/or improving the gastrointestinal properties of COX-2 selective inhibitors; for facilitating wound healing; for treating and/or preventing renal toxicity or other toxicities; for treating and/or preventing other disorders resulting from elevated levels of cyclooxygenase-2; and for improving the cardiovascular profile of COX-2 selective inhibitors.